REMARKS

Status of the Claims

Claims 1-110 are cancelled. Claims 111-146 were previously presented but not entered. Entry of these claims is not requested in the accompanying Request for Continued Examination (RCE) of the instant application.

Claims 147-210 are new. Support for these claims is found in the specification, for example, at page 11, lines 18-19; page 12, lines 1-3; page 59, line 24 through page 60, line 23; page 11, lines 18-19; page 12, lines 1-3; and page 59, line 24 through page 60, line 23.

No new matter is added.

Rejection of Claims 75-82, 84-94, 96-106 and 108-110 Under 35 U.S.C. § 112, First Paragraph

Claims 75-82, 84-94, 96-106 and 108-110 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification, while being enabling for antibodies that inhibit binding of the chemokines MIP-1α, MIP-1β, and RANTES to human CCR5, does not reasonably provide enablement for antibodies which inhibit binding of other chemokines to any mammalian CCR5. The Examiner further states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, the Examiner states that "a person of skill in the art is not enabled to make and use an antibody which inhibits binding of *any* 'chemokine' to *any* 'mammalian' CCR5" (Office Action, page 3, fourth paragraph, emphasis in original).

Applicants respectfully disagree. With respect to the Examiner's rejection regarding "any mammalian CCR5," Applicants note that the claims now presented recite a "human CCR5" and thus, this portion of the rejection is moot.

With respect to the Examiner's rejection regarding "any chemokine," Applicants submit that the specification as filed enabled one of skill in the art to make and use an antibody as claimed without undue experimentation. As stated in the MPEP, "the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation V. Hyde, 242 U.S. 261, 270 (1916), which postured the question:

is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)" (MPEP 8th edition, February 2003 revision, § 2164.01). Several factors are to be considered in determining if any experimentation is undue, including:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [*In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)]

Applicants submit that the quantity of experimentation necessary to make and use Applicants' claimed invention is merely routine for one of skill in the art when guided by Applicants' specification and what was known in the art at the time of filing. For example, Applicants have fully described and detailed in the specification methods of making and identifying antibodies that inhibit binding of a chemokine (such as, for example, MIP-1α, MIP-1β and RANTES) to CCR5 (see, Example 1, page 48, line 1 through page 53, line 22, Example 4, page 56, line 1 through page 64, line 25). Such assays would not be undue experimentation for one of skill in the art to perform, particularly as directed by Applicants and as described in the examples provided. Furthermore, members of the chemokine family are well-known in the art, as disclosed in the specification at page 1, line 9 through page 3, line 5. As also evidenced by Zlotnik and Yoshie (*Immunity 2000; 12:*121-127), and the classification system of chemokines described therein, CCR5 ligands were known in the art and could be classified accordingly. For example, CCR5 chemokines were known to include MIP-1α, MIP-1β and RANTES. The identification of other chemokines and their classification as chemokines that bind CCR5 requires only routine experimentation for one of skill in the art. Furthermore, Applicants provided in the specification assays to determine binding of a chemokine to CCR5 (see, for example, page 51, line 10 through page 52, line 26). Applicants also note that the scope of the claims is not unduly broad in view of Applicants' disclosure of chemokines that bind CCR5 which include MIP-1α, MIP-1β and RANTES, as compared to the number of chemokines that

bind CCR5 as identified by others, including Zlotnik and Yoshie, who also disclosed MIP-1α, MIP-1β and RANTES.

Thus, Applicants respectfully submit that, taken as a whole, in view of the breadth of the claims, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the examples of CCR5-binding chemokines provided by Applicants (see, for example, page 3, lines 2-5), the guidance and working examples by Applicants to determine if a chemokine binds CCR5 (see, for example, page 51, line 10 through page 52, line 26), and the amount of direction and working examples provided by Applicants to determine if an antibody to a human CCR5 inhibits binding of a chemokine to CCR5 (see, for example, page 62, line 5 through page 63, line 7), the specification clearly provides an enabling description for an antibody or antigen binding fragment thereof which inhibits binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to the receptor. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94, 96-106 and 108-110 Under 35 U.S.C. § 112, First Paragraph

Claims 75-82, 84-94, 96-106 and 108-110 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action, page 4, first paragraph).

Specifically, the Examiner states that:

> Applicant does not appear to have described what structural attributes make a mammalian protein a "CCR5" protein. Applicant does not appear to have described the common structural attribute that conveys function of chemokine binding to either human CCR5 in particular or any mammalian CCR5 in general. Absent a sufficient description of the receptor-ligand pairs, there consequently does not appear to be an adequate written description of the instantly recited genus of antibodies that bind only mammalian CCR5 and inhibit binding of the chemokine ligand of that species of CCR5. [Office Action, page 4, paragraph 5.]

The Examiner directs Applicants' attention to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, first paragraph "Written Description" Requirement, *Federal Register*, Vol. 66, No. 4, page 1099-1111, Friday, January 5, 2001.

Applicants respectfully disagree. Applicants also note that the Federal Register Written Description Guidelines are now incorporated into MPEP, 8th edition, February 2003 revision, § 2163.

The MPEP states that, for each claim drawn to a genus:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). [MPEP, 8th edition, February 2003 revision, page 2163-168, citations omitted]

As noted above, the claims now presented recite a "human CCR5" thus, the portion of the Examiner's rejection regarding "any mammalian CCR5" is moot.

With respect to the Examiner's remaining rejection, Applicants respectfully submit that the written description requirement for a claimed genus is satisfied through sufficient description of a representative number of species, wherein a representative number is an inverse function of the skill and knowledge in the art. (MPEP, 8th edition, February 2003 revision, § 2163). Applicants have provided examples of chemokines that bind CCR5, including, MIP-1α, MIP-1β and RANTES. As discussed above, Zlotnik and Yoshie evidence that the state of the art recognizes MIP-1α, MIP-1β and RANTES as chemokines that bind CCR5. In fact, Zlotnik and Yoshie only disclose these three chemokines. Thus, Applicants have described all of the three known chemokine species of the genus of chemokines that bind CCR5. Applicants have specifically provided examples of receptor-ligand pairs (*e.g.*, CCR5-MIP-1α; CCR5-MIP-1β; CCR5-RANTES) in contrast to the Examiner's assertion. Therefore, Applicants submit that they have fully met the written description requirement by providing a sufficient description of *a*

representative number of species, by actual reduction to practice, sufficient to show Applicants were in possession of the claimed genus (see, for example, page 62, line 5 through page 63, line 7). In addition, the mere recitation of a chemokine that binds CCR5 imparts sufficient description to one of ordinary skill in the art to appreciate which chemokines are envisaged by Applicants. Thus, the genus of CCR5-binding chemokines has adequate written description given the level of skill in the art, and the number of representative species provided by Applicants. Clearly, one of ordinary skill in the art would readily recognize that Applicants were in possession of the claimed invention at the time of filing of the application. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94 and 96-98 Under 35 U.S.C. § 102(e)

Claims 75-82, 84-94 and 96-98 are rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by Li *et al.* (U.S. Patent No. 6,025,154; IDS Ref. AE) *as evidenced by* Wu *et al.* (J. Exp. Med. 1997; 186(8):1373-1381; IDS Ref. AS4).

Specifically, the Examiner states that Li *et al.* explicitly teach assays for screening for antagonists of both ligand binding and receptor function associated with that binding (Office Action, page 5, paragraph 6).

Applicants respectfully disagree. The courts have consistently held that "[t]o serve as an anticipating reference, the reference must enable that which is it asserted to anticipate" *(Elan Pharmaceuticals, Inc. v Mayo Foundation for Medical Education and Research*, Fed. Cir. No. 00-1467, October 2, 2003); ("A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled" *Amgen, Inc. v. Hoechst Roussel, Inc.*, 314 F.3d 1313, 1354, 65 U.S.P.Q.2d 1385, 1416 (Fed. Cir. 2003)). In deciding whether or not a disclosure is enabled, the pertinent question is whether the experimentation needed to practice the invention is undue or unreasonable. As stated supra, the factors to be considered include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of

> the claims. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)

Li *et al.* does not disclose any chemokine as a CCR5 ligand. In fact, Li *et al.* does not disclose any ligand of CCR5. The state of the art at the time of Li *et al.* was such that no specific ligands of the receptor disclosed by Li *et al.* were known by Li *et al.* or by others. Li *et al.* were first to disclose the HDGNR10 receptor, and did not disclose any specific ligands of the receptor. Nor does Li *et al.* disclose any working examples of assays which could be used to identify antagonist antibodies. Thus, the lack of working examples, together with the lack of disclosure of any receptor ligand, means that the Li *et al.* assays which require the use of a receptor ligand to identify potential antibodies that bind to the receptor, cannot be performed by one of ordinary skill in the art based on the teachings of Li *et al.* without undue experimentation. As stated in *Elan* at page 8, "[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation." Thus, Li *et al.* is not an enabling reference for an antibody or antigen binding fragment thereof which binds to a human chemokine receptor 5 (CCR5), wherein said antibody or antigen binding fragment inhibits binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to the receptor. Without an enabling teaching of each and every aspect of Applicants' claimed invention, Li *et al.* is not anticipatory under 35 U.S.C. § 102.

Furthermore, contrary to the Examiner's assertion, the disclosure of antibodies by Li *et al.* is not *necessarily* a disclosure of each and every aspect of the claimed invention. Li *et al.* merely provides a generic statement that antibodies to the newly cloned HDGNR10 (CCR5) can be made. This disclosure by Li *et al.* does not allow one of ordinary skill in the art to "at once envisage" an antibody which binds CCR5, inhibits binding of a chemokine to CCR5 and inhibits one or more functions associated with binding of the chemokine to the receptor as recited in Claims 75-82, 84-94 and 96-98. Thus, the disclosure of Li *et al.* does not anticipate the claimed invention.

Li *et al.* disclose the identification of human G-protein chemokine receptor CCR5 and the DNA encoding the receptor. Li *et al.* also state that the receptor can be used as an immunogen to generate antibodies to the receptor using methods known in the art. Li *et al.* does not produce any antibodies to the disclosed receptor, and Li *et al.* do not teach or suggest any antibody or

antigen binding fragment which binds CCR5 and **inhibits** binding of a **chemokine** to CCR5, much less an antibody or antigen binding fragment which also inhibits one or more functions associated with binding of a chemokine to CCR5. Clearly the disclosure by Li *et al.* of the suggestion to make antibodies which bind CCR5 encompasses a myriad of antibody species having very different physical compositions and different functional properties. From this generic disclosure one of ordinary skill in the art would not immediately envisage a species of antibody which binds CCR5, inhibits binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to the receptor. It clearly not true that antibodies which bind CCR5 *necessarily* inhibit binding of a chemokine to the receptor and *necessarily* inhibit one or more functions associated with binding of the chemokine to the receptor as recited in the instant claims. These properties cannot be said to be inherent in an antibody which binds CCR5. Thus, contrary to the Examiner's assertion, Li *et al.* does not set forth disclosure of the presently claimed antibodies.

The Examiner has cited Wu *et al.* (*J. Exp. Med.* 186(8):1373-1381 (1997) as a secondary reference, which published after the priority date of the present application, apparently to show that characteristics not disclosed in the primary reference are inherent (MPEP, 8th edition, February 2003 revision, § 2131.01). However, such a showing requires that the secondary reference "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill" (MPEP, 8th edition, February 2003 revision, § 2131.01 III; citing *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991)).

Wu *et al.* does not fulfill this requirement. The Examiner stated in Office Action paper no. 14 that Wu *et al.* evidence that those antibodies which block binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5. This does not establish, however, that an antibody to CCR5 (as disclosed by Li *et al.*) would *necessarily* inhibit binding of a **chemokine** to CCR5 and *necessarily* inhibit one or more functions associated with binding of the **chemokine** to CCR5. Indeed, as discussed above, the premise that an antibody which binds CCR5 *necessarily* inhibits binding of a chemokine to the receptor and *necessarily* inhibits one or more functions associated with binding of the chemokine to the receptor is clearly false. It is indisputable that antibodies which bind CCR5 may not inhibit binding of chemokine

and/or inhibit one or more functions association with binding of chemokine to receptor (see, for example, Olson *et al., J. Virol.* 1999; *73(5)*:4145-4155). Thus, the functional properties recited in the instant claims are not inherent properties of the antibody disclosed by Li *et al.*, and the reference does not explicitly or impliedly teach or suggest all elements of the claimed invention. In sum, the disclosure of Li *et al.* does not provide an enabling disclosure to effectively identify the antibodies of the presently claimed invention, nor does the disclosure of Li *et al.* provide antibodies necessarily having each and every element of the claimed invention. As such, Li *et al.* is not an anticipatory reference.

In particular, Li *et al.* cannot anticipate a claim reciting inhibition of binding of any particular chemokine to CCR5, much less new Claims 149, 158-167, 170, 179-188, 191, or 200-210, which recite the specific chemokines MIP-1α, MIP-1β and RANTES.

Furthermore, Li *et al.* does not anticipate a claim reciting an antibody that binds to the second extracellular loop of CCR5, such as recited in new Claims 154, 164, 175, 185, 196 or 206. Li *et al.* does not disclose any particular regions of the CCR5 receptor protein to which an antibody may bind and clearly does not disclose a second extracellular loop as such a region. Nor is the ability to bind to the second extracellular loop necessarily a feature of the antibody allegedly disclosed by Li *et al.*, as there are many regions of the receptor protein to which an antibody could bind.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94 and 96-98 Under 35 U.S.C. §102(e)

Claims 75-82, 84-94 and 96-98 are rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by Hoxie (U.S. Patent No. 5,994,515; IDS Ref. AB) *as evidenced by* Olson *et al.* (*J. Virol.* 1999; 73:4145-4155; IDS Ref. AW5) and Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Specifically, the Examiner alleges that the screen taught in Hoxie that assayed for inhibition of HIV infection would necessarily result in antibodies that inhibited chemokine binding and one or more functions associated with chemokine binding to CCR5.

Applicants respectfully disagree. For anticipation under 35 U.S.C. § 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not

directly taught must be inherently present (MPEP, 8th edition, February 2003 revision, § 706.02). For a reference to anticipate by inherency, it is required that "the prior art *necessarily* functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (emphasis added). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co.USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis added). Hoxie does not explicitly teach or suggest every aspect of the invention of Claims 75-82, 84-94 and 96-98. Furthermore, Hoxie does not inherently teach each and every aspect of the claimed invention.

Hoxie teaches an "antiviral antibody" which binds to a cellular protein essential for entry of an immunodeficiency virus into a cell expressing that protein. The antibody disclosed by Hoxie is an "antiviral antibody" by virtue of its ability to inhibit entry of the immunodeficiency virus into a cell bearing the cellular protein by binding to the cellular protein (column 6, lines 21-31). Hoxie states that the cellular protein can be, for example, CCR5. However, it is noteworthy that Hoxie does not actually disclose the production of "antiviral" antibodies which bind to CCR5. In fact, the specific examples in Hoxie are directed solely to antibodies which bind to CXCR4 and which inhibit entry of the virus into the cell.

The claims of the subject application recite that the antibody or antigen binding fragment inhibits binding of a chemokine to the receptor, and inhibits one or more functions associated with binding of the chemokine to the receptor. This aspect of the invention is not taught or suggested by Hoxie, as Hoxie does not explicitly disclose an antibody or antigen binding fragment which binds CCR5, inhibits *chemokine* binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5.

Moreover, Hoxie does not inherently disclose an antibody or antigen binding fragment which binds CCR5, inhibits *chemokine* binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5. HIV viral co-receptor activity is dissociable from chemokine ligand-dependent signaling responses for CCR5. For example, Atchison *et al.* (*Science* 1996; 274:1924-1926) demonstrate that a chimera of the NH_2-terminus of human CCR5 fused to the remainder of human CCR2B retains vigorous function as a co-receptor for HIV-1 while exhibiting no detectable signaling response to cognate ligands for CCR5 or CCR2B (page

1925, column 3, lines 3-12). This data demonstrates that while the amino-terminal portion of CCR5 appears to be sufficient for CCR5 to function as a co-receptor for HIV, the amino terminal portion of CCR5 is not sufficient for chemokine response. Gosling *et al.* (*Proc. Natl. Acad. Sci. USA* 1997; 94:5061-5066) disclose that chimeras of CCR5 that failed to signal in response to chemokines remained fully functional as co-receptors for HIV (page 5061, col. 1, lines 24-26).

These publications demonstrate that HIV binds to a particular portion of the CCR5 receptor (the amino-terminus), while chemokines bind to a distinct portion of the receptor. The ability of an anti-CCR5 antibody to inhibit HIV entry into a CCR5-bearing cell is not coextensive with the ability of an anti-CCR5 antibody to inhibit chemokine binding to CCR5. In fact, the Examiner acknowledges that HIV co-receptor function and functions associated with chemokine binding to CCR5 can be dissociated. Thus, it is clear that an anti-CCR5 antibody which inhibits HIV entry into a CCR5-bearing cell does not inherently possess the ability to inhibit chemokine binding to CCR5 and/or the ability to inhibit one or more functions associated with binding of the chemokine to the receptor. Accordingly, Hoxie does not explicitly or impliedly disclose an antibody or antigen binding fragment which binds CCR5, inhibits chemokine binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5. Hoxie merely discloses one species of anti-CCR5 antibodies (which inhibits HIV entry into a CCR5-bearing cell). This suggestion to make this species does not anticipate the species of anti-CCR5 antibody recited in the subject application (which inhibits chemokine binding to CCR5 and inhibits one or more functions associated with binding of chemokine to receptor).

The Examiner again cites two secondary references, Olson *et al.*, and Wu *et al.*, to show that characteristics that were not disclosed in Hoxie are inherent in the monoclonal antibodies of Hoxie. The Examiner stated in paper no. 14 that Wu *et al.* evidence that those antibodies which block binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5. In the Office Action made Final (Paper no. 19), the Examiner again states that Olson *et al.* show that the antibodies most effective at inhibiting HIV membrane fusion and viral entry (assays of HIV infection) are the antibodies that also inhibit calcium flux in response to the chemokine RANTES binding to CCR5, and thus the screen taught in Hoxie that assayed for antibodies which inhibit HIV infection would necessarily identify antibodies that inhibited chemokine binding and one or more functions associated with chemokine binding to

CCR5. This assertion is not true however. The teaching that the antibodies most effective at inhibiting HIV entry also inhibit chemokine binding *does not mean* that an antibody which inhibits HIV entry as disclosed by Hoxie would *necessarily* have the properties recited in the instant claims. Moreover, the fact that the screen taught by Hoxie would *identify* antibodies which inhibit both HIV membrane fusion and viral entry and calcium flux in response to RANTES binding **if** such antibodies were present does **not** mean that an antibody with these characteristics would *necessarily* be produced by the described methods. An antibody which inhibits CCR5-mediated HIV entry into a cell is not *necessarily* an antibody which inhibits binding of a chemokine to CCR5 and inhibits one or more functions associated with binding of the chemokine to the receptor. Thus, because Hoxie does not teach every aspect of the claimed invention either explicitly or impliedly, Hoxie does not anticipate the invention of Claims 75-82, 84-94 and 96-98. In particular, Hoxie cannot anticipate a claim reciting inhibition of binding of any particular chemokine to CCR5, much less new Claims 149, 158-167, 170, 179-188, 191, or 200-210, which recite the specific chemokines MIP-1α, MIP-1β and RANTES.

Furthermore, Hoxie does not anticipate a claim reciting an antibody that binds to the second extracellular loop of CCR5, such as recited in new Claims 154, 164, 175, 185, 196 or 206. Hoxie does not disclose any particular regions of the CCR5 receptor protein to which an antibody may bind and clearly does not disclose a second extracellular loop as such a region. Nor is the ability to bind to the second extracellular loop necessarily a feature of the antibody allegedly disclosed by Hoxie as there are many regions of the receptor protein to which an antibody could bind.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94, 96-106 and 108-110 Under 35 U.S.C. §102(e)

Claims 75-82, 84-94, 96-106 and 108-110 are rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by Littman *et al.* (U.S. Patent No. 5,939,320; IDS Ref. AA) *as evidenced by* Olson *et al.* (*J. Virol.* 1999; 73:4145-4155, IDS Ref. AW5) and Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Specifically, the Examiner alleges that a screen such as taught in Littman *et al.* that assayed for inhibition of HIV infection would necessarily include antibodies that inhibited

chemokine binding and one or more functions associated with chemokine binding to CCR5 because those were the antibodies most effective at inhibiting HIV infection.

Applicants respectfully disagree. As already stated, for anticipation under 35 U.S.C. § 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present (MPEP, 8th edition, February 2003 revision, § 706.02). For a reference to anticipate by inherency, it is required that "the prior art *necessarily* functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (emphasis added). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co.USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). Littman *et al.* does not teach or suggest every aspect of the invention of Claims 75-82, 84-94, 96-106 and 108-110, nor are each and every element of the claimed invention inherent in Littman *et al.*

Littman *et al.* teach the identification and application of an agent which is capable of promoting the translocation of M-tropic HIV through the membrane of a target CD4+ cell (*e.g.*, CCR5), as well as agents (*e.g.*, antibodies) which are able to inhibit this translocation. Littman *et al.* do not produce any such antibodies. Moreover, Littman *et al.* do not disclose any antibodies, much less anti-CCR5 antibodies, which inhibit binding of a chemokine to a chemokine receptor and which inhibit one or more functions associated with binding of chemokine to receptor. Thus, Littman, *et al.* does not explicitly disclose an antibody or antigen binding fragment which binds CCR5, inhibits chemokine binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5.

Furthermore, Littman *et al.* also does not impliedly disclose an antibody or antigen binding fragment which binds CCR5, inhibits chemokine binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5. As discussed above with regard to the §102 rejection over Hoxie, the Examiner has acknowledged that HIV viral co-receptor activity is dissociable from chemokine ligand-dependent signaling responses for CCR5. It is clear that antibodies which can inhibit the entry of HIV into CCR5-bearing cells are not *necessarily* able to inhibit binding of a chemokine to CCR5 and/or inhibit one or more functions associated with binding of chemokine to CCR5. Littman *et al.* does not teach or suggest any

antibodies which bind CCR5, inhibit binding of a chemokine to CCR5 and inhibit one or more functions associated with binding of a chemokine to CCR5 as recited; indeed, Littman *et al.* does not produce any anti-CCR5 antibodies which could even be assessed for such functions. Littman *et al.* merely states that its disclosure relates to an antibody which is able to inhibit entry of HIV into a cell bearing, e.g., CCR5. This disclosure does not explicitly or impliedly anticipate the invention of the subject claims, which recite an antibody which binds CCR5, inhibits binding of a chemokine to CCR5, and inhibits one or more functions associated with binding of chemokine to CCR5. Again, Applicants direct the Examiner's attention to the holding of the courts that for primary and secondary reference:

> There must be no difference between the claimed invention and the reference disclosure, as viewed by a person or ordinary skill in the field of the invention. It is sometimes appropriate to consider extrinsic evidence to explain the disclosure of a reference...The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, **not to fill gaps in the reference.** *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q. 2d 1001, 1010 (Fed. Cir. 1991) (emphasis added).

The Examiner has again cited Wu *et al.* (*J. Exp. Med.* 186(8):1373-1381 (1997) as a secondary reference, which published after the priority date of the present application to evidence that antibodies which block binding of chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5. As Littman *et al.* do not disclose any antibodies, much less anti-CCR5 antibodies, which inhibit binding of a chemokine to a chemokine receptor and which inhibit one or more functions associated with binding of chemokine to receptor, the Wu *et al.* reference cannot evidence that Littman *et al.* teaches an antibody which binds CCR5, inhibits binding of a chemokine to CCR5 and inhibits one or more functions associated with binding of a chemokine to CCR5 or that binds to the second extracellular loop of CCR5.

The Examiner has also cited Olson *et al.* (*J. Virol.* 1999; 73:4145-4155) as a secondary reference to evidence that the antibodies reported to be most effective at inhibiting HIV membrane fusion and viral entry are the antibodies that also inhibit calcium flux in response to the chemokine RANTES binding to CCR5. However, as discussed *supra*, Littman *et al.* does not teach or suggest *any* antibodies which bind CCR5, inhibit binding of a chemokine to CCR5 and

inhibit one or more functions associated with binding of a chemokine to CCR5 as recited in the appealed claims. Therefore, the teaching of Olson *et al.* does not mean that any antibodies of Littman *et al.* will *necessarily* be antibodies that inhibit calcium flux in response to the chemokine RANTES binding to CCR5. Thus, the functional properties recited in the instant claims are not inherent properties of the antibody disclosed by Littman *et al.*, and the reference does not explicitly or impliedly teach or suggest all elements of the claimed invention.

In sum, the disclosure of Littman *et al.* does not provide an enabling disclosure to effectively identify the antibodies of the presently claimed invention, nor does the disclosure of Littman *et al.* provide antibodies necessarily having each and every element of the claimed invention. As such, Littman *et al.* is not an anticipatory reference. More particularly, Littman *et al.* cannot anticipate a claim reciting inhibition of binding of any particular chemokine to CCR5, much less new Claims 149, 158-167, 170, 179-188, 191, or 200-210, which recite the specific chemokines MIP-1α, MIP-1β and RANTES.

Furthermore, Littman *et al.* does not anticipate a claim reciting an antibody that binds to the second extracellular loop of CCR5, such as recited in new Claims 154, 164, 175, 185, 196 or 206. Littman *et al.* does not disclose any particular regions of the CCR5 receptor protein to which an antibody may bind and clearly does not disclose a second extracellular loop as such a region.

Reconsideration and withdrawal of the rejections are respectfully requested.

Rejection of Claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 Under 35 U.S.C. §103(a)

Claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 are rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Chuntharapai *et al.* (U.S. Patent No. 5,543,503; IDS Ref. AD) in view of either Raport *et al.* (*J. Biol. Chem. 271*:17161-17166 (1996); IDS Ref. AW), Samson *et al.* (*Biochem. 35*:3362-3367 (1996); IDS Ref. AV), or Combadiere *et al.* (*J. Leukoc. Biol. 60*:147-152 (1996); IDS Ref. AT3), as evidenced by Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Specifically, the Examiner states that Chuntharapai *et al.* teach that antagonist antibodies can also be screened for their ability to block activation of IL-8R-expressing cells, citing column 30, especially lines 20-31, and column 2, especially lines 33-41.

Applicants respectfully disagree. *In re Vaeck* sets forth a two-prong standard for establishing combined reference obviousness; both prongs of the test must be met in order for such a rejection to be proper. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to those of ordinary skill in the art that they should...carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. *Id. at n re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Additionally, the cited references must teach or suggest all of the claim limitations. "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* None of the combinations based on the cited references teaches or suggests the claimed invention. Moreover, no reasonable expectation of success founded in the prior art exists with respect to the claimed antibodies as discussed in detail below.

Chuntharapai *et al.* teach at column 30, lines 20-31, an "IL-8 antagonist antibody that binds to an epitope of the FIG. 2 receptor that is shared by the Murphy and Tiffany receptor" (column 30, lines 23-25). Chuntharapai *et al.* go on to further teach that "[a]ntibodies that inhibit IL-8 activation **or** binding to **both** cells are then selected as the therapeutic candidates (column 30, lines 29-31; emphasis added). At column 2, lines 33-41, Chuntharapai *et al.* teach an antibody that binds an IL-8 receptor, has an IgG1 isotype and/or neutralizes the *in vitro* activity of an IL-8 receptor. Chuntharapai *et al.* do not teach an antibody to CCR5 that inhibits chemokine binding to the receptor and which inhibits one or more functions associated with binding of the chemokine to the receptor. Chuntharapai *et al.* do not even teach an antibody which binds to the IL-8 receptor and inhibits IL-8 binding to the receptor and inhibits one or more functions associated with binding of IL-8 to the receptor.

Raport *et al.* describe the identification and characterization of cDNA encoding CCR5 and disclose that the encoded receptor binds RANTES, MIP-1α and MIP-1β. Raport *et al.* do not teach or suggest antibodies to the CCR5 receptor, nor do they teach or suggest antibodies which can inhibit the binding of a chemokine to CCR5 and inhibit function associated with binding of chemokine to receptor.

Samson *et al.* teach the cloning of a human gene encoding chemokine receptor CCR5 and assess the physiological responses to various chemokines mediated by CCR5. The reference

does not disclose any anti-CCR5 antibodies and does not teach or suggest the production of anti-CCR5 antibodies, including those which inhibit binding of a chemokine to CCR5 and inhibit one or more functions associated with binding of chemokine to receptor.

Combadiere *et al.* teach the cloning of a CCR5 variant whose amino acid sequence differs from the amino acid sequence of CCR5 disclosed by Samson *et al.* at amino acid 90. Once again, Combadiere *et al.* do not teach or suggest antibodies to CCR5 which inhibit binding of a chemokine to CCR5 and inhibit function associated with binding of chemokine to receptor.

Applicants respectfully submit that the combination of Chuntharapai *et al.* with Raport *et al.*, Samson *et al.* and Combadiere *et al.* does not teach or suggest all of the limitations of the instant claims as required for a proper rejection under 35 U.S.C. § 103 because even the combination of references does not teach or suggest an anti-CCR5 antibody which inhibits binding of a chemokine to CCR5 and inhibits one or more functions associated with binding of the chemokine to the receptor. None of the cited references teaches or suggests any antibodies which are able to inhibit one or more functions associated with binding of a chemokine to its receptor, let alone anti-CCR5 antibodies which have the requisite functional inhibitory properties.

Chuntharapai *et al.* merely discloses an anti-IL-8R antibody which inhibits binding of IL-8 to IL-8R but does not additionally disclose the functional effect of this inhibition. The determination that an antibody is able to inhibit binding of IL-8 to IL-8R does not mean that antibody is able to inhibit one or more functions associated with binding of the chemokine (*e.g.*, IL-8) to receptor (*e.g.*, IL-8R). As disclosed in Olson *et al.* and in the Declaration by Walter Newman, Ph.D., under 37 C.F.R. § 1.132 (previously submitted by Applicants as Exhibit A with Amendment A, filed at the U.S. Patent and Trademark Office on April 11, 2003), antibodies which inhibit binding of a chemokine may themselves trigger receptor function by virtue of their binding to the receptor (Olson *et al.*, page 4147, column 2, lines 46-48; Declaration, paragraph 6). In this instance, inhibition of binding of the chemokine to the receptor would not inhibit the biological activities of the receptor which result from binding of the chemokine, as some or all of these activities can be potentiated by the antibody itself. The fact that an antibody which is capable of inhibiting binding of a chemokine to receptor can have several effects on the functions associated with binding of chemokine to receptor is evidenced by Frade *et al.* (*J. Immunol.* 1997;

159(11):5576-5584). Frade *et al.* discloses the production of a panel of monoclonal antibodies capable of binding CCR2 as demonstrated by the fact that all six mAbs recognize THP-1 and Mono Mac 1 cells, as well as CCR2-transfected 293 cells, in flow cytometry analysis. However, an assessment of the functional effects of binding of these antibodies to the CCR2 receptor showed a widely varied functional response. Some antibodies had no effect on function in chemotaxis and calcium flux assays. Other antibodies (antagonists) inhibited one or the other of the assessed functions, while a third group of antibodies (agonists) caused an increase from baseline in one or more of the assessed functions. Thus, it is highly unpredictable from the mere disclosure of antibodies which inhibit the binding of chemokine (*e.g.*, IL-8) to receptor (*e.g.*, IL-8R) what the effect, if any, of such an antibody will be on functions associated with binding of the chemokine to receptor. Despite their statement that functional blocking antibodies can be produced, in view of their failure to assess the functional activities of their antibodies, Chuntharapai *et al.* cannot be fairly summarized as teaching an antibody which inhibits on or more functions associated with binding of a chemokine to its receptor, and the secondary references do not remedy this defect.

Thus, Applicants respectfully submit that the Examiner has not established a *prima facie* showing of obviousness under 35 U.S.C. § 103 because all of the claim limitations are not taught or suggested by the cited art.

Even assuming *arguendo* that the references were properly combined, the teachings of the cited references do not establish a reasonable expectation of success in obtaining the anti-CCR5 antibodies with the requisite activity for a number of reasons.

First, CCR5 is distinct from IL-8 receptor. The prior art does <u>not</u> teach that CCR5 is equivalent to IL-8 receptor and in fact, CCR5 is <u>not</u> equivalent to the IL-8RA and IL-8RB receptors. Thus, there would be no reasonable expectation of success in making antibodies which both inhibit binding of chemokine to the CCR5 protein and inhibit one or more functions associated with binding of chemokine to CCR5 founded upon the teachings related to anti-IL-8RA/RB antibodies as disclosed by Chuntharapai *et al.*, since the prior art does not teach that CCR5 is equivalent to IL-8RA or IL-8RB, and because IL-8RA/RB and CCR5 are not in fact equivalents. CCR5 has a distinct primary amino acid sequence and a different structure and function from IL-8RA and IL-8RB. For example, studies with IL-8 receptors and antibodies

thereto would have no bearing on the question of whether CCR5 chemokine binding regions might be immunogenic, and thus there would be no reasonable expectation of success in obtaining anti-CCR5 antibodies which inhibit chemokine binding.

As discussed in the previously submitted Declaration by Walter Newman, Ph.D., it is very difficult to obtain antibodies to chemokine receptors such as CCR5. Moreover, the ability of an antibody to inhibit binding of a ligand to a receptor is dependent upon many factors. For example, one or more structural elements which are involved in ligand binding must be capable of inducing an immune response. The location of such epitopic regions within a protein is difficult to predict, and there is no reasonable expectation that the ligand binding regions of the receptor protein will be epitopic regions. Furthermore, even if the ligand binding regions are immunogenic, the resulting antibody may not interfere with the binding of a ligand to the receptor. For example, the portion of the receptor which binds to a ligand (*e.g.*, a chemokine) may have a conformation which allows binding of both the ligand and antibody.

As discussed above, there is no reasonable expectation of success in producing antibodies to CCR5, and even if such an antibody is produced, there is no reasonable expectation that the antibody will inhibit binding of a ligand to the receptor. Moreover, as stated in the concurrently submitted copy of the Declaration, there is no reasonable expectation that the antibodies which are obtained will inhibit one or more functions associated with binding of the ligand to the receptor. Antibodies can function as agonists or antagonists of receptor function. That is, antibodies which bind to a particular receptor and inhibit binding of a ligand to the receptor can inhibit the function associated with the binding of the ligand to the receptor, or can induce or enhance the function associated with binding of the ligand to the receptor. Thus, antibodies which act as agonists of receptor function can "mimic" the effect of ligand binding and cause the same or increased downstream effects as binding of the ligand.

The previously filed copy of the Declaration provides additional evidence regarding the production of anti-CCR5 antibodies which supports the lack of a reasonable expectation of success in producing antibodies to CCR5 which inhibit binding of a ligand to the receptor and which inhibit one or more functions associated with binding of the ligand to the receptor. In the Declaration, Dr. Newman states that approximately 17 different hybridoma fusions were screened, two of which produced antibodies reactive with CCR5 transfectants. One of these

fusions provided approximately 25 CCR5-reactive supernatants, about one-half of which were followed up with subcloning and further analysis. One of these produced approximately two reactive supernatants, one of which produced antibody 2D7 described in the application. Thus, prior to the present invention there was no reasonable expectation of success in producing antibodies which inhibit binding of a ligand to CCR5 and which inhibit one or more functions associated with binding of the ligand to the receptor, as such antibodies were very difficult to obtain.

Additionally, Olson *et al.* (*J. Virol.* 1999; 73(5):4145-4155) generated a number of anti-CCR5 murine monoclonal antibodies (PA8, PA9, PA10, PA11, PA12 and PA14), all of which were able to inhibit HIV-1 envelope-mediated membrane fusion; all of these antibodies blocked fusion between CD4+ CCR5+ PM1 cells and HeLa- $Env_{JR\text{-}FL+}$ cells in a RET assay. However, of these antibodies, only PA14 blocked calcium mobilization induced by the chemokine RANTES, and the calcium mobilization inhibiting activity of monoclonal antibody 2D7 was superior to that of PA14 (Figures 3A and 3B of Olson *et al.*).

In view of the foregoing, it is clear that the requirements needed to establish the obviousness of the claimed invention in light of the cited references under *In re Vaeck* have not been met. For these reasons, Applicants respectfully submit that the combination of Chuntharapai *et al.*, Raport *et al.*, Samson *et al.* and Combadiere *et al.* does not render the subject invention obvious because the cited references, alone or in combination, do not teach or suggest all elements of the claimed invention and do not provide the ordinarily skilled artisan with a reasonable expectation of success in producing the claimed invention. Furthermore, the Examiner's reliance on Wu *et al.* as evidence to support the obviousness rejection has apparently been based on improper hindsight reasoning, which is impermissible (MPEP, 8th edition, February 2003 revision, § 2142).

Furthermore, Chuntharapai *et al.* does not make obvious a claim reciting inhibition of binding of any particular chemokine to CCR5, much less new Claims 149, 158-167, 170, 179-188, 191, or 200-210, which recite the specific chemokines MIP-1α, MIP-1β and RANTES.

Further still, Chuntharapai *et al.* does not make obvious a claim reciting an antibody that binds to the second extracellular loop of CCR5, such as recited in new Claims 154, 164, 175, 185, 196 or 206. Chuntharapai *et al.* does not disclose any particular regions of the CCR5

receptor protein to which an antibody may bind and clearly does not disclose a second extracellular loop as such a region.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 80-82, 86, 92-94, 98, 104-106 and 110 Under 35 U.S.C. §103(a)

Claims 80-82, 86, 92-94, 98, 104-106 and 110 are rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Chuntharapai *et al.* (U.S. Patent No. 5,543,503; IDS Ref. AD) in view of either Raport *et al.* (*J. Biol. Chem. 271*:17161-17166 (1996); IDS Ref. AW), Samson *et al.* (*Biochem. 35*:3362-3367 (1996); IDS Ref. AV), or Combadiere *et al.* (*J. Leukoc. Biol. 60*:147-152 (1996); IDS Ref. AT3), as evidenced by Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4), as applied to claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 above; and further in view of Ramakrishnan *et al.* (U.S. Patent No. 5,817,310).

Applicants respectfully disagree. Chuntharapai *et al.,* Raport *et al.*, Samson *et al.*, Combadiere *et al.*, and Wu *et al.*, have been discussed *supra.*

Ramakrishnan *et al.* disclose immunoglobulins (antibodies) and fragments thereof that bind to PDGF beta receptor (see, for example, Abstract and columns 8-9). Ramakrishnan *et al.* do not teach or suggest single chain, Fab, $F(ab')_2$ or chimeric antibodies that bind to a human CCR5, and which inhibit binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to the receptor. The disclosure of antibody fragments and chimeric antibodies which specifically bind to a human type beta PDGF receptor does not render obvious antibody fragments or chimeric antibodies which specifically bind a different receptor, and inhibit ligand binding to that receptor, and inhibit one or more functions associated with binding of the ligand to that receptor.

As discussed *supra*, Chuntharapai *et al.* with Raport *et al.*, Samson *et al.*, or Combadiere *et al.* and as evidenced by Wu *et al.*, do not teach or suggest all of the limitations of the instant claims. The teachings of Ramakrishnan *et al.*, fail to remedy these deficiencies. Thus, Ramakrishnan *et al.*, either alone or in combination with the other cited references, do not render the presently claimed invention obvious.

Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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